International Journal of Pancreatology, vol. 25, no. 3, 251, June 1999

0169-4197/99/25:251/$10.25

Letters to the Editor

The "Two-Hit" Pathogenetic Concept of Chronic Pancreatitis

To the Editor:

We have read with interest the recent state-of-the-art article on chronic pancreatitis (CP) presenting a new working model *(1)*. The author postulates that the first even in CP is duct cell dysfunction, documented histologically by intraductal "protein plugs," followed by a perturbation of acinar cell function and activation of digestive enzymes within the pancreatic gland.

The various concepts on pathophysiology of CP have been critically reviewed at a recent international workshop on alcoholic CP, which was attended by about 40 well-recognized experts in this field *(2)*. The experts agreed that the relationship between acute pancreatitis and CP in relation to the underlying etiology is an important and yet unsettled issue. Although acute "biliary" pancreatitis virtually never progresses to CP, alcoholic acute pancreatitis seems to evolve into CP in many instances, although a small percentage of alcoholic acute pancreatitis probably will not show progression to CP *(2)*. The long-held view that alcoholic acute pancreatitis regularly occurs on the basis of pre-existent CP has, according to the experts, not been substantiated by unequivocal data *(2,3)*. It was also believed that the "protein plug" hypothesis is debatable and should not be accepted as a proven concept for the pathogenesis of CP *(2)*. In fact, "protein plugs" were observed histologically in a large series of CP predominately in advanced CP (i.e., in 88.4% of cases with a fibrosis score > 7, compared to 45.5% of cases with mild fibrosis < 6) *(3)*. In early-stage CP, in contrast, focal autodigestive necrosis and/or postnecrotic pseudocysts, which are the morphological hallmmarks of acute pancreatitis, were the prominent features *(3)*.

The new working model of CP proposed by Freedman *(1)* relies basically on a doubtful marker of "early" events in CP, i.e., protein plugs and neglects the prominent feature of necrosis, which predominates in early-stage CP *(3)*. The "necrosis-fibrosis" hypothesis postulates that there is a second factor, i.e., postnecrotic fibrosis involving the ductal system and thereby promoting the evolution to CP *(2,3)*. It seems likely that the pathophysiology of CP depends basically on "two hits," as suggested *(1–3)*, one each at the "acinar" and the "ductal" level. The arguments in support of a first hit at the "ductal" level as suggested by Freedman *(1)* are challenged by the "necrosis-fibrosis" hypothesis *(2,3)*, which indicates that the primary event (i.e., first hit) probably occurs at the "acinar" level.

R. W. Ammann
Division of Gastroenterology,
Department of Internal Medicine,

Ph. U. Heitz
Department of Pathology,
University Hospital, Zurich, Switzerland,

G. Klöppel
Department of Pathology,
University of Kiel, Germany

References

1 Freedman St D. New concepts in understanding the pathophysiology of chronic pancreatitis. *Int J Pancreatol* 1998; 24: 1–8.
2 Ammann RW. A clinically based classification system for alcoholic chronic pancreatitis: summary of an international workshop on chronic pancreatitis. *Pancreas* 1997; 14: 215–221.
3 Ammann RW, Heitz Ph U, Klöppel G. Course of alcoholic chronic pancreatitis: a prospective clinico-morphological long-term study. *Gastroenterology* 1996; 111: 224–231.